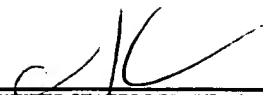




UNITED STATES PATENT AND TRADEMARK OFFICE


UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

09/723,722

11/28/2000

John P. Anderson

00228-US-NEW2C1

9856

20350

7590

01/19/2006

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

WALICKA, MALGORZATA A

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

09/723,722

Applicant(s)

ANDERSON ET AL.

Examiner

Malgorzata A. Walicka

Art Unit

1652

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 October 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 03 October 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): none.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 1, 15, 18, 22-25, 29-31, 36 and 132-134.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

The Amendment After Final filed Oct 3, 2005 is acknowledged. Claims 1, 15, 18, 22-25, 29-31, 33-34, 36, and 132-134 are pending and are the subject of this Advisory Action.

1. Rejection under 35 USC section 103 (a)

Claims 1, 15, 18 and dependent claims 22 and 132-134 remain rejected for the reasons explained in the Office Action of June 30, 2005 as being unpatentable over US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998, in view of the common knowledge in molecular biology and in the field of aspartyl proteases as exemplified by the review article by Tang J. et al. (Evolution in Structure and Function of Aspartyl Proteases, Journal of Cellular Biochemistry, 1987, 33, 53-63).

Claims 23-25, 29-31, 33-34 and 36 remain rejected for the reasons explained in the Office Action of June 30, 2005 as being unpatentable over US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998, in view of the common knowledge in molecular biology and in the field of aspartyl proteases as exemplified by the review article by Tang J. et al. (Evolution in Structure and Function of Aspartyl Proteases, Journal of Cellular Biochemistry, 1987, 33, 53-63) and further in the view of the article by Viswandhan V. et al. (An Approach to Rapid Estimation of Relative Binding Affinities of Enzyme Inhibitors: Application to Peptidomimetics Inhibitors of the Human immunodeficiency Virus Type 1 protease, J. Med. Chem. 1996, 39, 705-712).

2. *Nonstatutory double patenting rejection*

The non-provisional obviousness-type double patenting rejections of claim 1, over claims 1, 2, and 6 of US Patent No. 5,744,346 are maintained, because Applicants did not file a terminal disclaimer or amended the claim. The rejected claim reads on the purified, native, mature form of human beta-secretase. The native mature form was purified in the patent, although not to the homogeneity.

Traversing this rejection Applicants argue, the last paragraph on page 7 of REMARKS/ARGUMENTS,

“Common general knowledge is not a sufficient reason to establish obviousness for the *de novo* isolation of a protein to apparent homogeneity from a natural source. Although purification of proteins from recombinant sources is often routine because such proteins can be expressed at high levels, and with tags to facilitate affinity purification, the same is not necessarily true for purification of proteins from natural sources. Many proteins of interest are expressed only in a very low levels, and the purification process is empirical in nature, as was discussed in the last response. Bet-secretase in particular has proved elusive. There has been an number of earlier reports purporting to purify this enzyme that are now recognized as having purified something else (see Pennisi, Science 286, 650 (1999) (copy attached))².”

Applicants conclude in the third paragraph on page 8 that to establish *prima facie* obviousness is the burden on the Examiner, because, merely citing to common general

knowledge is not enough to fulfill the burden of proof that beta- secretase could have been routinely purified to homogeneity from a natural source.

The Applicants' arguments have been fully considered but are found not persuasive for the following reasons. Firstly, as opposite to the arguments, according to the Applicants and Inventors purification of beta secretase is routine for the following reasons:

- a) US Patent No. 5,744,346, column 4, line 44, "it is preferred that beta-secretase be obtained from cellular sources using known protein purification techniques".
- b) provisional application 60/110,571 from which the instant application claims priority, teaches on page 31, line 15:

"Beta-secretase can be recovered and purified from recombinant cell cultures by any of number of methods well known in the art, including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, and lectin chromatography".

Although this refers to the purification of recombinant beta- secretase the listed

Art Unit: 1652

methods, with exception of affinity purification that may be facilitated, are routinely used to isolate native proteins.

In addition, beta-secretase is not expressed in low level, as the Applicants argue. The simplest extraction of membranes by Triton solution provides extracts that are used to determine its presence in many tissues; see the Inventor's article Nature, 1999, 402, Dec. 2, 1999, page 537 the last paragraph, and Fig. 2 on page 378; included in Information Disclosure Statement.

Thus, it is not the examiner, whose opinion is that purification of beta- secretase is obvious, but the Applicants themselves.

Secondly, the quoted article by Pennisi uses the term "elusive beta-secretase" in the following context:

"Over the last 5 years, at least a dozen teams have described candidates for an elusive enzyme called beta-secretase, which is needed to free one end of beta-amyloid from its larger precursor protein, known as APP (for amyloid precursor protein). No candidates have swayed the Alzheimer's research community, and many have already failed to stand the test of time", page 650 left column, second paragraph.

The quoted passage relates to difficulties with identifying a candidate enzyme and not to purification of beta-secretase to homogeneity after it has been identified. The passage does not report difficulties or "elusiveness" of purifying beta-secretase to homogeneity. Only one other passage in Pennisi's article relates to the subject: "Hunting for a specific protein-splitting enzyme is extremely difficult, since cells are loaded with hundreds of

Art Unit: 1652

these proteases", page 650, middle column, second paragraph. However, this passage relates to difficulties in identifying a specific protease in general, but not to purification of beta-secretase to homogeneity after it has been identified.

In summary, as explained in the previous Office Actions, patentability of a product is dependent on the characteristics of the product itself and not on its method of making. Both products, the one of claims of the instant application and that of claims in the patent possess the same enzymatic characteristics and source of origin independently of the method of their purification. Although the method of purification in the patent and in the instant application are different, these are the products that are claimed and not the methods of their isolation.

3. Conclusion


Claims 1, 15, 18, 22, 23-25, 29-31, 33-34 and 36 and 132-134 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1652

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1800
1652